# CROSS-SENSITIVITY BETWEEN STREPTOMYCIN AND DIHYDROSTREPTOMYCIN*

FREDERICK J. WENZEL, B.S. AND STEPHAN EPSTEIN, M.D.

Conflicting reports about cross-sensitivity between streptomycin and dihydrostreptomycin (DHS) prompted us to study this problem under controlled conditions in sensitized guinea pigs.

## MATERIALS AND METHODS

Albino guinea pigs weighing between 400 to 500 grams were used in groups of 10 animals. They were prepared by four weekly subcutaneous injections of 5 mgm of streptomycin or DHS, respectively, mixed with Freund's adjuvant. One week after the last preparatory injection, the animals were tested intradermally with 0.1 cc of 1% solutions of both streptomycin and DHS. The animals later on were tested with a 1% solution of streptidine; patch tests with 10% solutions of these chemicals were also carried out.

Commercial streptomycin and dihydrostreptomycin were used†. Streptomycin can be considered a pure preparation; however commercial DHS contains about 3% streptomycin because it is produced from streptomycin by reduction. According to the U.S.P. a 3% contamination of DHS with streptomycin is permissible. Our own studies utilizing the maltol method (1, 2) confirmed an admixture of 3% streptomycin. We purified the commercial DHS by recrystallization so that the contamination was only 1%.

## RESULTS

All animals prepared with streptomycin became allergic to this drug and gave strong delayed-type reactions to intradermal tests; in most of them patch tests were also positive. The intradermal tests were characterized by indurated papules 15 mm in diameter, exhibiting a marked erythema. Numerous histologic examinations confirmed the allergic nature of the reactions. The histologic descriptions of these tests have been presented elsewhere (3). Control tests on non-sensitized animals produced no reactions at all or only minor pink papules less than 7 mm in diameter.

Guinea pigs sensitized to streptomycin did not react to DHS or streptidine. Of the more than 30 animals prepared with DHS none became allergic to this drug. However, in our first series 5 out of 8 animals prepared with commercial DHS gave a delayed-type reaction to intradermal tests with streptomycin. We suspected contamination of DHS with streptomycin as the cause of this strange behavior and could demonstrate that the contaminating amount of streptomycin was sufficient to sensitize. Of 10 guinea pigs which had been sensitized with the corresponding amount of streptomycin (0.15 mgm as contrasted to the 5 mgm in the original series) 3 animals became allergic. When we attempted to sensitize guinea pigs with a more purified DHS (containing only 1% streptomycin) only 1 animal out of 7 reacted. It is regrettable that we had no streptomycin-free DHS available for this study. But the drop in the number of sensitized animals corresponds well with the decreased amounts of streptomycin utilized for the sensitization. Therefore these findings may be considered adequate evidence that the "DHS guinea pigs" had been sensitized by the contaminating streptomycin.

## DISCUSSION AND COMMENTS

Our studies show that there is no cross-sensitivity between streptomycin and DHS in guinea pigs. This is also supported by our previous studies (2) on cross-sensitivity between neomycin and streptomycin; guinea pigs sensitized to neomycin cross-reacted with streptomycin, but not with DHS.

A survey of the literature, and of personal communications from several physicians with wide experience in the treatment of tuberculosis, indicates that in general cross-sensitivity between the two drugs is rare. This lack of cross-sensitivity is surprising because, as Figure 1 shows, streptomycin and DHS are very closely related chemically. The difference between the two drugs lies in the streptose part of the molecule. In DHS the aldehyde group of streptomycin is reduced to an alcohol group. Apparently such a minor chemical change is the reason for the great difference in the

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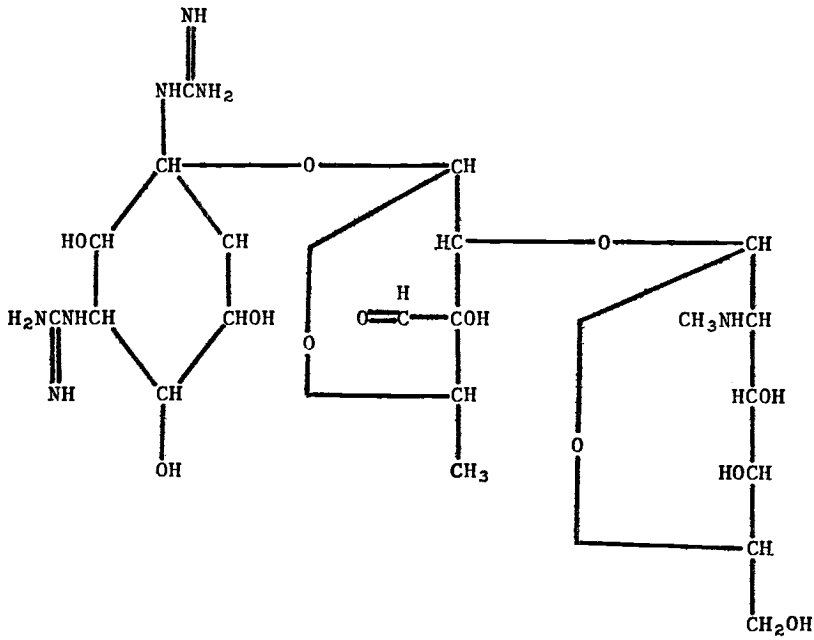
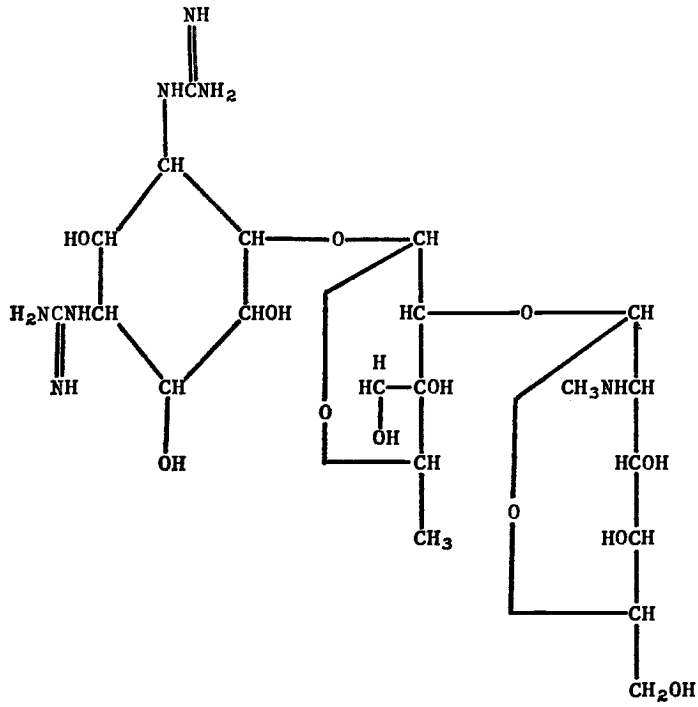



STREPTOMYCIN




DIHYDROSTREPTOMYCIN

FIG. 1. Structural formulas of Streptomycin and Dihydrostreptomycin

sensitization potential of these two drugs. Streptomycin is notoriously a very potent sensitizer; DHS is not. Among others, Hilt and Roederer (4) emphasize the non-sensitizing character of DHS. There are however some reports that claim cross-sensitivity between streptomycin and DHS in humans. Miller (5) as well as Sulzberger (6) reported on patients who were allergic to streptomycin and who also reacted to dihydrostreptomycin. These authors assumed that there was cross-sensitivity between the two drugs because their patients had not been previously exposed to DHS. Simon (7, 8) also claimed cross-sensitivity. However, all these authors apparently were not aware that commercial DHS is contaminated with streptomycin. An analysis of their data strongly suggests the possibility that the reactions to tests with commercial DHS were not an expression of cross-sensitivity, but rather were due to the contaminating streptomycin or to independently developed sensitivity to DHS. The degree of sensitivity to streptomycin in nurses suffering from contact dermatitis apparently is very high. Wilson (9) reports that 3 out of 6 streptomycin-sensitive nurses gave positive patch tests to 0.01% dilutions. A 1% patch test with commercial DHS would contain streptomycin in sufficient concentration to cause a positive patch test in a highly sensitive person. Absence of cross-sensitivity between streptomycin and DHS is also suggested by Hobson, *et al.* (10). These authors treated 5 streptomycin sensitive patients with purified DHS without any sign of sensitivity. They observed negative patch tests to DHS in a number of streptomycin sensitive patients. Livingood (11) also reported negative intradermal tests to dihydrostreptomycin in 4 streptomycin sensitive patients. It appears therefore that reports about cross-sensitivity between streptomycin and DHS cannot be considered valid unless the patients gave also positive reactions to purified DHS. By the same token, reports about sensitization following the use of crude DHS (10) do not necessarily prove sensitization to this chemical because, like our guinea pigs, the patient may have become sensitized to the contaminating streptomycin.

SUMMARY

1) Guinea pigs can be sensitized to streptomycin, but not to dihydrostreptomycin (DHS).

2) Cross-sensitivity between these two antibiotics does not occur in guinea pigs.

3) Reactions to streptomycin in guinea pigs prepared with DHS are due to contamination of commercial DHS with streptomycin.

4) It seems doubtful that cross-sensitivity between streptomycin and DHS exists in man. Analysis of reports on cross-sensitivity between streptomycin and DHS in man suggests that the few reported instances of positive reactions to DHS in nurses with streptomycin contact sensitivity may have been due to the contaminating streptomycin found in commercial DHS, or may represent independently acquired sensitivity to DHS.

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